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10/553,169	11/28/2005	Roger R. C. New	117-565	7760

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NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
HA, JULIE	

ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,169	NEW, ROGER R. C.	
	Examiner	Art Unit	
	JULIE HA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 January 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-7,9-14,19-24,26-33,36-38,41 and 42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 5-7, 9-14, 19-24, 26-33, 36-38 and 41-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment after Non-final rejection filed on January 19, 2010 is acknowledged. Claims 39-40 have been cancelled. Claims 1-2, 5-7, 9-14, 19-24, 26-33, 36-38 and 41-42 are pending and examined on the merits in this application.

The Declaration under 37 CFR 1.132 filed January 19, 2010 is insufficient to overcome the rejection of claims 1-2, 5-7, 9-14, 19-24, 26-33, 36-38 and 41-42 based upon 35 U.S.C. 103(a) as set forth in the last Office action because: the declaration fails to set forth facts. The Declaration appears to be stating an opinion from the Applicant.

Withdrawn Objections and Rejections

1. Objection to claim 40 and 42 are hereby withdrawn in view of Applicant's cancellation of claim 40 and amendment to claim 42.

2. Claims 9-11 and 19-21 rejected under 35 U.S.C. 112, second paragraph, as being indefinite is hereby withdrawn in view of Applicant's amendment to the claims.

3. Claims 9-11 and 19-21 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with written description is hereby withdrawn in view of Applicant's amendment to the claims.

Maintained Rejection

35 U.S.C. 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. Claims 1-2, 5-7, 9-14, 19-24, 26-33, 36-38 and 41-42 remain rejected under 35 U.S.C. 103(a) as being unpatentable over New (US Patent No. 5,853,748) in view of Desai (US Patent No. 5,206219) and Sonnenberg & Kotchen (Curr. Op. Neph. Hyperten., 1998, 7, 551-555).

7. New teaches a pharmaceutical composition of (i) a biologically active proteinaceous material, oligonucleotide or analogue there of or polysaccharide; (ii) a bile acid or salt; and (iii) an agent having the ability to adjust the pH of the gut to a value of from 7.5 to 9 (see claim 1). New teaches specific example of macromolecular principle (insulin), a bile acid (chenodeoxycholic acid) and an additive that buffers the gut to pH 7.5-9 (sodium bicarbonate, example 4), meeting the limitation of claims 9-11

and 19-21. New teaches that sodium carbonate or bicarbonate can increase the solubility of the bile acids (see column 6, lines 4-7), and thus increase the permeability of bioactive through epithelial cells (see column 6, lines 4-19). New further teaches a composition with an enteric coating designed to prevent digestion in the stomach and to permit digestion in the small intestine (see column 7, lines 37-40), meeting the limitation of claims 31-35. New teaches a method of enhancing the absorption of the insulin across the intestinal wall in an animal body comprising administering the insulin/chenodeoxycholic acid/sodium bicarbonate composition, meeting the limitation of claims 24, 26, 32 and 35. Further, the composition comprises less than 5% by weight of water (see table in example 4), meeting the limitations of claims 2 and 22. New teaches that the additive, sodium bicarbonate, is present at 8.3% by weight which is greater than 1% (table in Example 4). The ratio by weight of the chenodeoxycholic acid plus the additive to the insulin is 10:1 which is greater than 5:1 (table in Example 4). New teaches that the quantity of bile acid contained in a single dose of the formulation will vary depending on the particular bile acid chosen and the rate and extent to which that bile acid dissolves in the aqueous fluid contained in the intestine. For chenodeoxycholic acid, and most other bile acids, this is likely to be within range 10 mg to 1 g, preferably between 20 mg to 200 mg (most preferably 30 mg to 100 mg). For deoxycholic acid, the maximum will generally not exceed 500 mg, in view of slightly greater activity (see column 3, lines 49-57).

New teaches that the composition is in the form of a solution (see column 7, lines 5-55) or a solid (example 4), meeting the limitation of claims 6-7 and 23. The

composition sensitizes the subject to insulin by increasing uptake (see example 4), meeting the limitation of claims 11 and 21. The non-conjugated bile acid is chenodeoxycholic acid, the acid form of chenodeoxycholate. New teaches that in general, bile salts start to be converted to their conjugate acid at pH of about 6.8 or below and the acid form is insoluble in aqueous solutions. New teaches that the buffering agent has the effect of buffering the compositions of the composition at a pH of about 7.5 or above, the solubilized bile salt will be present rather than the insoluble bile acid. A solubilized bile salt will be able to act on the epithelial cells when in solution, whereas this may not be possible in the solid acid form (see column 6, lines 6-14). Furthermore, New teaches that the higher the concentration of buffering agent, the more rapidly will a satisfactory pH be attained, resulting in more rapid dissolution of the bile acid or salt, resulting in a higher local concentration of the bile salt in solution, leading to greater efficacy in enhancing permeability to bioactive materials (see column 6, lines 14-19). The reference further teaches that the composition is dispersed in water (see for example, claim 8), meeting the limitation of new claims 36-37. The difference between the reference and the instant claims is that the reference does not teach propyl gallate or butyl hydroxyl anisole (BHA) and further addition of insulin sensitizing agent.

8. However, Desai teaches that other adjuvants for preserving the formulations are common in pharmaceutical formulations and antioxidants like butylated hydroxyanisole (BHA), butylated hydroxytoluene, d-α-tocopherol, and propyl gallate are commonly used in pharmaceutical compositions of insulin and other protein active ingredients (see column 5, lines 5-18). Typical antioxidant concentrations can be used which is usually a

standard practice; these can be from 0.1% to 1.5% (w/w or w/v). Desai further teaches a dosage unit pharmaceutical composition, adapted for oral administration, containing as active proteinaceous ingredients erythropoietin, insulin growth hormones, calcitonin, GCSF, cyclosporine, vasopressin or its agonists and antagonists...interferons or interleukins (see column 2, lines 13-18, and Examples 1-4).

9. Furthermore, Sonnenberg & Kotchen teach that troglitazone has been approved by the FDA for the treatment of type II diabetes. Sonnenberg & Kotchen teach that troglitazone produced a significant, dose-dependent reduction in glycosylated hemoglobin and fasting glucose concentrations despite decreases in insulin doses in clinical trials involving diabetic patients (see page 552).

10. It would have been obvious to one of ordinary skill in the art to add in antioxidants or preservatives, such as butyl hydroxyl anisole (BHA) or propyl gallate, since these additives are commonly used for preserving the pharmaceutical formulation, and prevent degradation, to enhance the longer shelf life of the proteinaceous ingredients. Furthermore, since New teaches the presence of sodium bicarbonate had beneficial effect by increasing the solubility of the bile acids to soluble bile salts and enhanced the permeability to bioactive materials (see New column 6, lines 4-7 and lines 17-19). Therefore, since New teaches the increased solubility of the bile acid or salt by sodium bicarbonate and teaches the pharmaceutical composition comprising an active macromolecule (insulin) and a non-conjugated bile acid or salt and sodium bicarbonate, it would have been obvious to add a well known antioxidant to preserve the pharmaceutical formulation. Since combination of sodium bicarbonate (additive)

increased the solubility of the bile acid, then combination of a known antioxidant into the formulation would also have the same solubility. One of ordinary skill in the art would have been motivated to add in the antioxidants or preservatives to the pharmaceutical composition since these adjuvants would preserve the formulation, prevent degradation, and thus increase the shelf life of the pharmaceutical composition.

Further, it would have been obvious to one of ordinary skill in the art to maintain the pH of the intestinal fluid between pH 6.8 to 7.5, since New teaches that bile salts start to convert to its conjugate acid at pH of about 6.8 or below, and the acid form is insoluble in aqueous solution, and the buffering agent has the effect of buffering the compositions of the invention to a pH of about 7.5 or above, in which the solubilized bile salt will be present rather than the insoluble acid. One would be motivated to maintain the pH of the intestinal fluid not above pH 7.0, since New teaches that the bile salts begin to be converted to their conjugate acid at pH of about 6.8 or below and the acid form is insoluble in aqueous solutions (see New column 6, lines 6-8). New additionally teaches that the pH of the gut is between 5 to7 (see column 4, lines 17-19). A solubilized bile salt will be able to act on the epithelial cells when in solution. There is a reasonable expectation of success, since the New reference teaches enhanced permeability of the bioactive agents by solubilizing the bile acids using the sodium bicarbonate, thus addition of an antioxidant (that prevents the degradation of peptide or protein in the pharmaceutical formulation) would also have the same solubility. Further, maintaining the intestinal fluid between pH 6.8 and 7.0 would allow the bile salt to be in the soluble salt non-conjugated form to act on the epithelial cells when in solution in the

intestinal fluid, which will lead to greater efficacy in enhancing permeability to bioactive materials, such as insulin and other protein drugs.

Additionally, it would have been obvious to add a known insulin sensitizing agent in the pharmaceutical composition, since Sonnenberg & Kotchen teach that troglitazone has been approved by the FDA for the treatment of type II diabetes. One of the ordinary skilled in the art would have been motivated to add a known insulin sensitizing agent in the pharmaceutical composition, since Sonnenberg & Kotchen teach that troglitazone produced a significant, dose-dependent reduction in glycosylated hemoglobin and fasting glucose concentrations despite decreases in insulin doses in clinical trials involving diabetic patients. There would have been a reasonable expectation of success, since the FDA has approved the use of troglitazone in combination with insulin, and has been shown to work in clinical trials involving diabetic patients. Therefore, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Applicant's Arguments

11. Applicant argues that "in the Declaration (see section 2 to 9), '748 describes bicarbonate compositions, the whole point of which is to form an aqueous solution during use. '219, on the other hand, teaches the use of a microemulsion containing fatty globules. It is simply not credible to suggest that a skilled person wishing to help preserve the '748 bicarbonate composition would have sought the answer in '219...the skilled person would have considered adding a well-known water soluble preservative,

such as vitamin C, sodium metabisuphite or malic acid." Applicant argues that "no skilled person would have contemplated adding PG or BHA to the bicarbonate compositions of '748…In the Declaration (see sections 12 to 14), PG and BHA have low solubility in water. The skilled person would have known that PG or BHA would be likely to prejudice the formation of an aqueous solution…Adding PG or BHA stops the '748 bicarbonate compositions from working." Applicant further argues that "as noted in section 15 of the Declaration, even if the skilled person had been shown document '219, they would still not have been motivated to add PG or BHA to the '748 bicarbonate composition, because '219 simply confirms that these additives are only suitable for use with oil or fat".

In the Declaration filed on January 19, 2010, Applicant argues that "I believe there is crucial difference between the teaching of '748 and '219, namely that '748 is concerned with providing an aqueous solution of bile salt plus bicarbonate in the intestine, whereas '219 teaches to provide a microemulsion with fatty globules. On this basis, I do not believe that a person of ordinary skill in the art seeking to help preserve a bicarbonate-containing composition of '748 would have sought the answer in '219." Applicant further argues that "I believe that a person of ordinary skill in the art would have realized that to avoid disturbing the important aqueous solution formed by '748 compositions, the only preservatives with a chance of being viable would be ones that are readily soluble in water." Applicant argues that "I certainly do not believe that a person of ordinary skill in the art would have contemplated adding PG or BHA to a '748 composition. PG and BHA both have very poor solubility in water and so are typically

used only in oils or fats." Applicant argues that "I believe that a person of ordinary skill in the art would have assumed that adding PG or BHA would prevent the '748 composition from forming the crucial aqueous solution in the intestines...earlier Declaration confirms that if PG or BHA is added to a solution of bile acid and bicarbonate, this leads to a turbid dispersion, even after incubation at 60ºC." Furthermore, Applicant argues that "I believe that the person of ordinary skill in the art would still not have been led to add PG or BHA. That is because, rather than displacing the above-mentioned assumption that PG or BHA would prevent the '748 composition from forming the crucial aqueous solution, the '219 document actually reinforces it. Thus, the paragraph from lines 6 to 28 of '219 confirms that PG and BHA should only be used in fatty/oily environments – they are mentioned specifically in connection with the lipid component of the '219 compositions. The only preservatives from '219 that a person of ordinary skill in the art might have contemplated adding to a '748 composition, are the hydrophilic ones mentioned at lines 25 and 26 of column 5."

12. Applicant's arguments have been fully considered, but have not been found persuasive.

The primary reference (New) teaches a pharmaceutical composition comprising an active macromolecular polypeptide (insulin), a non-conjugated bile acid or salt (in the range of 10 mgs to 1 g) and an additive (sodium bicarbonate). New teaches that the amount of bile acid will vary depending on the particular bile acid chosen and the rate and extent to which that bile acid dissolves in the aqueous fluid contained in the intestine. The most preferred amount for chenodeoxycholic acid was from 30 mg to 100

mg (see column 3, lines 52-55). The addition of sodium bicarbonate increased the solubility of the bile salt, thereby increasing the permeability of the bioactive agents across the cell wall. Therefore, addition of a well known antioxidant (preservative) would have the same solubility. Additionally, the claim recites that "when introduced into the intestine, does not raise the pH of the intestinal fluid above pH 7.0." This is the function of the solid pharmaceutical composition. The claims further recite, "wherein the additive is capable of allowing the non-conjugated bile acid or salt to remain in solution..." This implies that the function may or may not occur. Thus, since the combined arts teach all of the active components of the instant composition, this composition "is capable of allowing the non-conjugated bile acid or salt to remain in solution." Claim 1 does not recite that the pharmaceutical composition and the active agents must be in certain amounts or concentrations. Furthermore, claim 1 does not recite that there is no fat or oil present in the solid composition. Claim 2 recites that there is less than 5% by weight of water. Desai reference teaches that "the amount of any water is limited to 5% of the polyol solvent" (see Example 1). Additionally, claim 6 recites that "the mixture is in the form of a solution or a microparticulate dispersion". Desai teaches proteinaceous medicaments formulated for oral administration as liquid as well as a filled hard or soft gelatin (see abstract). Desai also teaches microemulsion, which is a species of microparticulate dispersion. Therefore, one of ordinary skill in the art would have been motivated to add in antioxidants or preservatives, such as butyl hydroxyl anisole (BHA) or propyl gallate, since these additives are commonly used for preserving the

pharmaceutical formulation, and prevent degradation, to enhance the longer shelf life of the proteinaceous ingredients.

In regards to the 132 declaration, this declaration states an opinion from Dr. New. The declaration does not provide any evidentiary basis. The MPEP states the following: "Applicant may submit factual affidavits under 37 CFR 1.132 or cite reference to show what one skilled in the art knew at the time of filing the application. A declaration or affidavit is, itself, evidence that must be considered. The weight to give a declaration or affidavit contains support the conclusion of enablement. *In re Bechner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991) ("expert opinion on the ultimate legal conclusion must be supported by something more than a conclusory statement") See MPEP 2164.05.

Applicant is reminded that claim 1 is drawn to a solid pharmaceutical composition. The primary reference (New) teaches a pharmaceutical composition comprising a macromolecular polypeptide (insulin), a non-conjugated bile acid or salt, and an additive (sodium bicarbonate) that increases the solubility of the non-conjugated bile acid, thus enhancing the permeability of the bioactive molecule. An addition of a well known antioxidant to the pharmaceutical composition that would preserve the formulation would have the same solubility, since the pharmaceutical composition having the sodium bicarbonate already increased the solubility of the bile acid. Since the pharmaceutical composition is in a solid form, it does not matter that the formulation would precipitate out at pH 6.8. The New reference teaches that "bile salts start to be converted to their conjugate acid at pH of about 6.8 or below and the acid form is

insoluble in aqueous solutions, it would have been obvious to one or ordinary skill in the art to maintain the pH of the intestinal fluid in between pH 6.8 to 7.5. New reference teaches that the pH of the gut is between 5 to 7, therefore, one would have been motivated to maintain the pH of about 7. Furthermore, one of ordinary skill in the art would have been motivated to combine the well known antioxidant to the pharmaceutical formulation, since the secondary reference (Desai) teaches that these adjuvants preserve the pharmaceutical formulation, thus increasing the shelf-life of the proteinaceous bioactive agents. Since sodium bicarbonate increases the solubility, and antioxidants are known to increase the shelf-life of the bioactive agents, one of ordinary skill in the art would have been motivated to use together, to achieve the optimal proteinaceous bioactive agent composition. In regards to Applicant's argument that "I believe that a person of ordinary skill in the art would have realized that to avoid disturbing the important aqueous solution formed by '748 compositions, the only preservatives with a chance of being viable would be ones that are readily soluble in water," again, the claims are drawn to a solid pharmaceutical composition, not to a solution. Furthermore, Desai teaches that other adjuvants for preserving the formulations are common in pharmaceutical formulations (see column 5, lines 6-7) and some of the oil soluble antioxidants listed are butylated hydroxyanisole, butylated hydroxytoluene, d-α-tocopherol, propyl gallate, etc (see column 5, lines 16-18). The examples show different biologically active peptides (see column 2, lines 13-18), such as insulin and d-α-tocopherol (part of the oil soluble antioxidant) (see Example 1); erythropoietin and d-α-tocopherol (see Example 2); human growth hormone and d-α-

tocopherol (see Example 3); calcitonin and d-α-tocopherol (see Example 4). Therefore, one of ordinary skill in the art would have been motivated to use any of the oil soluble antioxidants listed. Again, the claims do not recite that only water was utilized in the mixture of (a) + (b) + (c). Other solvent and components can be in the mixture of (a) + (b) + (c). Further, the components (a) and (b) may already be in a solubilized form. There is no indication that (a) and (b) did not form a soluble formulation, and then the addition of (c) would form a solid composition, or after the addition of (c), the composition was solidified or purified.

Conclusion

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). No claim is allowed.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Julie Ha/
Examiner, Art Unit 1654